

☒ L4: (444394) INDOLINONE COMPOUNDS
☒ L5: (2732) INDOLINONE COMPOUNDS and
☒ L7: (2479) 16 and 11
☒ L9: (234978) endothelial cells
☒ L10: (11576) endothelial cells and
☒ L11: (520343) smooth muscle cells
☒ L12: (330876) smooth muscle cells
☒ L13: (29350) tyrosine kinase
☒ L14: (22929) tyrosine kinase and 1
☒ L15: (20606) tyrosine kinase and 1
☒ L8: (2287) 16 and 11 and inhibits
☒ L6: (2711) INDOLINONE COMPOUNDS and

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INDOLINONE COMPOUNDS and 13 and 12

☒ BRS form ☒ IS&R form ☒ Image ☒ Text

| | U | Document ID | Issue Dat | Pages | Title | Current OR | Current XR | Retrieval | Inv |
|------|-------------------------------------|-------------|-----------|-------|-------------------------|------------|------------|-----------|------------------|
| 1930 | <input type="checkbox"/> | US 5661126 | 19970826 | 64 | Use of mullerian | 514/12 | 435/68.1 | | Donahoe, K. |
| | <input type="checkbox"/> | A | | | | | ; 435/69.1 | | |
| 1931 | <input checked="" type="checkbox"/> | US 5660827 | 19970826 | 83 | Antibodies that bind to | 424/152.1 | 424/130.1 | | Thorpe, . et al. |
| | <input type="checkbox"/> | A | | | endoanlin | | ; 424/138. | | |
| 1932 | <input checked="" type="checkbox"/> | US 5659013 | 19970819 | 9 | Vascular permeability | 530/350 | 530/387.1 | | Senger, . et al. |
| | <input type="checkbox"/> | A | | | factor targeted compoun | | ; 530/387. | | |
| 1933 | <input checked="" type="checkbox"/> | US 5658894 | 19970819 | 19 | Compositions for | 514/58 | 514/21 | | Weisz, P |
| | <input type="checkbox"/> | A | | | inhibiting restenosis | | ; 514/23 | | |
| 1934 | <input checked="" type="checkbox"/> | US 5658791 | 19970819 | 67 | Antibodies which | 435/331 | 435/338 | | Wilks, A |
| | <input type="checkbox"/> | A | | | specifically bind to pr | | ; 530/387. | | Frederic |
| 1935 | <input checked="" type="checkbox"/> | US 5658758 | 19970819 | 30 | Polynucleotides | 435/69.1 | 435/252.3 | | Ni, Jian |
| | <input type="checkbox"/> | A | | | encoding cytostatin I | | ; 435/320. | | . et al. |
| 1936 | <input checked="" type="checkbox"/> | US 5658756 | 19970819 | 34 | CDNA encoding a novel | 435/69.1 | 435/193 | | Rodan, G |
| | <input type="checkbox"/> | A | | | human protein tyrosine | | ; 435/252. | | . et al. |
| 1937 | <input checked="" type="checkbox"/> | US 5658594 | 19970819 | 4 | Method of producing | 424/537 | 424/571 | | Al-Hassa |
| | <input type="checkbox"/> | A | | | wound healing preparati | | ; 424/572 | | M. |
| 1938 | <input checked="" type="checkbox"/> | US 5658592 | 19970819 | 21 | Medical crosslinked | 424/488 | 514/944 | | Tanihara |
| | <input type="checkbox"/> | A | | | polymer gel of carboxyl | | ; 516/102 | | . et al. |
| 1939 | <input checked="" type="checkbox"/> | US 5658570 | 19970819 | 47 | Recombinant antibodies | 424/184.1 | 435/69.6 | | Newman, |
| | <input type="checkbox"/> | A | | | for human therapy | | ; 435/70.2 | | . et al. |
| 1940 | <input checked="" type="checkbox"/> | US 5656655 | 19970812 | 10 | Styryl-substituted | 514/415 | 548/505 | | Spada, A |
| | <input type="checkbox"/> | A | | | heteroarvl compounds wh | | | | . et al. |
| 1941 | <input checked="" type="checkbox"/> | US 5656654 | 19970812 | 26 | Arylidene and | 514/412 | 514/307 | | Buzzetti |
| | <input type="checkbox"/> | A | | | heteroarvlidene oxindol | | ; 514/314 | | . et al. |
| 1942 | <input checked="" type="checkbox"/> | US 5656643 | 19970812 | 20 | Bis mono-and bicyclic | 514/312 | 514/313 | | Spada, A |
| | <input type="checkbox"/> | A | | | arvl and heteroarvl com | | ; 514/314 | | . et al. |
| 1943 | <input checked="" type="checkbox"/> | US 5656605 | 19970812 | 8 | Device to promote | 514/21 | 424/423 | | Hansson, J |
| | <input type="checkbox"/> | A | | | drug-induced nerve rege | | ; 424/426 | | . et al. |



- L4: (444394) INDOLINONE COMPOUNDS
- L5: (2732) INDOLINONE COMPOUNDS and
- L7: (2479) 16 and 11
- L9: (234978) endothelial cells
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- L13: (29350) tyrosine kinase
- L14: (22929) tyrosine kinase and 1
- L15: (20606) tyrosine kinase and 1
- L8: (2287) 16 and 11 and inhibits
- L6: (2711) INDOLINONE COMPOUNDS and

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DBs: USPAT

Default operator: OR

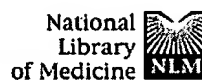
Plurals Synonyms

Highlight all hit terms initially

INDOLINONE COMPOUNDS and 13 and 12

BRS form IS&R form Image Text

| U | Document ID | Issue Dat | Pages | Title | Current OR | Current XR | Retrieval | Inv |
|------|-------------|-----------|-------|-------------------------|------------|------------|-----------|----------|
| 1970 | US 5650415 | 19970722 | 23 | Quinoline compounds | 514/312 | 514/313 | | Tang, Pe |
| | A | | | | | : 546/153 | | . et al. |
| 1971 | US 5650313 | 19970722 | 32 | Ubiquitin conjugating | 435/193 | 435/252.3 | | Ni, Jian |
| | A | | | enzymes 8 and 9 | | : 435/320. | | . et al. |
| 1972 | US 5650293 | 19970722 | 35 | Nucleic acid encoding | 435/69.1 | 435/252.3 | | White, M |
| | A | | | pp60.suo.PIK and the me | | : 435/320. | | |
| 1973 | US 5650267 | 19970722 | 27 | Method of detecting | 435/5 | 435/235.1 | | Ray, Bry |
| | A | | | compounds utilizing gen | | : 435/320. | | . et al. |
| 1974 | US 5650148 | 19970722 | 114 | Method of grafting | 424/93.2 | 424/93.21 | | Gage, Fr |
| | A | | | genetically modified ce | | : 435/948 | | . et al. |
| 1975 | US 5650135 | 19970722 | 33 | Non-invasive | 424/9.1 | 424/193.1 | | Contag, |
| | A | | | localization of a light | | : 424/258. | | Christoc |
| 1976 | US 5648357 | 19970715 | 40 | Enantiomerically pure | 514/263 | 514/267 | | Bianco, |
| | A | | | hydroxylated xanthine c | | : 514/270 | | . et al. |
| 1977 | US 5648334 | 19970715 | 42 | Methods of treatment | 514/12 | 514/2 | | Davis, S |
| | A | | | using ciliary neurotrop | | : 530/350 | | . et al. |
| 1978 | US 5648217 | 19970715 | 19 | DNA sequence which | 435/6 | 435/69.8 | | Levy, Da |
| | A | | | binds transcriptional r | | : 435/7.1 | | |
| 1979 | US 5646261 | 19970708 | 30 | 3'-derivatized | 536/24.3 | 536/24.5 | | Uhlmann, |
| | A | | | oligonucleotide analogs | | | | . et al. |
| 1980 | US 5646251 | 19970708 | 39 | Alloreaction-associated | 530/350 | 435/69.1 | | Ruegg, C |
| | A | | | antigen (ARAG): a novel | | : 530/324 | | . et al. |
| 1981 | US 5646153 | 19970708 | 56 | Bis mono- and bicyclic | 514/259 | 514/248 | | Spada, A |
| | A | | | arvl and heteroarvl com | | : 514/249 | | . et al. |
| 1982 | US 5646117 | 19970708 | 9 | Therapeutic agent for | 514/12 | 424/85.1 | | Matsushi |
| | A | | | treating wounds using m | | : 424/85.2 | | . et al. |
| 1983 | US 5646109 | 19970708 | 25 | Convertible | 514/2 | 424/400 | | Owen, Al |
| | A | | | microemulsion formulati | | : 514/12 | | . et al. |



| | | | | | | | |
|---------------|---|---------------|--------|-----------|--------|-----------|-------|
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- ☐ 1: Liu ZY, Ganju RK, Wang JF, Schweitzer K, Weksler B, Avraham S, Groopman JE.

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Blood. 1997 Sep 15;90(6):2253-9.

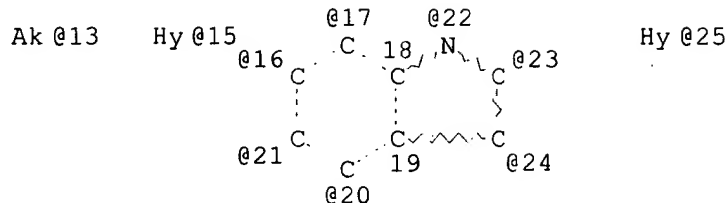
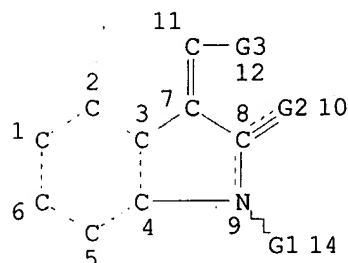
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L5 STR



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VAR G3=22/23/24/20/21/16/17/25/15
NODE ATTRIBUTES:
CONNECT IS E1 RC AT 13
DEFAULT MLEVEL IS ATOM
GGCAT IS MCY UNS AT 25
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E4 C E1 N AT 15
ECOUNT IS E4 C E1 S AT 25

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NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE
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FILE 'HCAPLUS' ENTERED AT 09:47:15 ON 24 MAY 2001

L7 ~~844S L6~~
L8 21787 S VEGF OR PDGF OR FGF OR (VASCULAR ENDOTHELIAL OR PLATELET
DERI
L9 64218 S PROLIFER? OR ANTIPROLIF?

FILE 'STNGUIDE' ENTERED AT 09:50:24 ON 24 MAY 2001

FILE 'HCAPLUS' ENTERED AT 09:58:32 ON 24 MAY 2001

L10 37 S L7 AND (L8 OR L9)
L11 ~~8 S L7 AND L8 AND L9~~ *claim 2 w/ keywords*
L12 29 S L10 NOT L11
L13 ~~7 S L12 AND (63/SC, SX OR PHARMA?)~~ *- claim other pharmaceutical*

FILE 'REGISTRY' ENTERED AT 10:00:40 ON 24 MAY 2001 *Too many structures to*

FILE 'HCAPLUS' ENTERED AT 10:01:06 ON 24 MAY 2001 *print out*

=> d .ca hitstr l11 1-8;d .ca hitstr l13 1-7

L11 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:153502 HCAPLUS

TITLE: Inhibition of the VEGF receptor 2 combined with chronic hypoxia causes cell death-dependent pulmonary endothelial cell **proliferation** and severe pulmonary hypertension

AUTHOR(S): Taraseviciene-Stewart, Laimute; Kasahara, Yasunori; Alger, Lori; Hirth, Peter; McMahon, Gerald; Waltenberger, Johannes; Voelkel, Norbert F.; Tudor, Rubin M.

CORPORATE SOURCE: Department of Pathology, Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Health Sciences Center, Denver, CO, 80262, USA

SOURCE: FASEB J. (2001), 15(2), 427-438
CODEN: FAJOEC; ISSN: 0892-6638 -

PUBLISHER: Federation of American Societies for Experimental
Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Our understanding of the pathobiol. of severe pulmonary hypertension, usually a fatal disease, has been hampered by the lack of information of its natural history. We have demonstrated that, in human severe pulmonary

hypertension, the precapillary pulmonary arteries show occlusion by proliferated endothelial cells. Vascular endothelial growth factor (VEGF)

and its receptor 2 (VEGFR-2) are involved in proper maintenance, differentiation, and function of endothelial cells. We demonstrate here that VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by proliferating endothelial cells. Prior to and concomitant with the development of severe pulmonary hypertension, lungs of chronically hypoxic SU5416-treated rats show significant pulmonary endothelial cell death, as demonstrated by activated caspase 3 immunostaining and TUNEL. The broad caspase inhibitor Z-Asp-CH2-DCB prevents the development of intravascular pulmonary endothelial cell growth and severe pulmonary hypertension caused by the combination of SU5416 and chronic hypoxia.

CC 14-5 (Mammalian Pathological Biochemistry)

ST VEGFR chronic hypoxia pulmonary hypertension artery cell
proliferation

IT Proteins, specific or class

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(Akt; VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT Transcription factors

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(Src; VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT Apoptosis

Cell death

Cell **proliferation**

Lung

(VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT Hypoxia, animal

(chronic; VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT **Vascular endothelial growth factor**
receptors

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(gene KDR; VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT Artery
(pulmonary, endothelium; VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

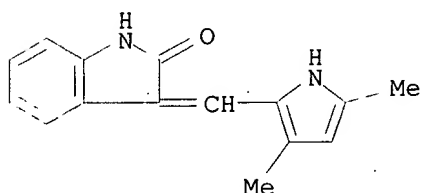
IT Hypertension
(pulmonary; VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT 204005-46-9, SU5416
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT 169592-56-7, caspase 3
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

IT 204005-46-9, SU5416
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension assocd. with precapillary arterial occlusion by **proliferating** endothelial cells)

RN 204005-46-9 HCAPLUS
CN 2H-Indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 32

REFERENCE(S):

- (1) Alon, T; Nature Med 1995, V1, P1024 HCAPLUS
- (2) Barst, R; N Engl J Med 1996, V334, P296 HCAPLUS
- (4) Daemen, M; J Clin Invest 1999, V104, P541 HCAPLUS
- (5) Dimmeler, S; Cell Death Differ 1999, V6, P964 HCAPLUS
- (6) Feng, Y; Biochem Biophys Res Commun 1999, V256, P192 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:417312 HCAPLUS

DOCUMENT NUMBER: 133:159618

TITLE: Identification of Substituted 3-[(4,5,6,7-Tetrahydro-1H-indol-2-yl)methylene]-1,3-dihydroindol-2-ones as

Page 7

Growth Factor Receptor Inhibitors for **VEGF**
-R2 (Flk-1/KDR), FGF-R1, and PDGF
-R.beta. Tyrosine Kinases

AUTHOR(S): Sun, Li; Tran, Ngoc; Liang, Congxing; Hubbard, Steve; Tahg, Flora; Lipson, Kenneth; Schreck, Randall; Zhou, Yong; McMahon, Gerald; Tang, Cho

CORPORATE SOURCE: SUGEN Inc., South San Francisco, CA, 94080-4811, USA

SOURCE: J. Med. Chem. (2000), 43(14), 2655-2663
 CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of new 3-substituted indolin-2-ones contg. a tetrahydroindole moiety was developed as specific inhibitors of receptor tyrosine kinases assocd. with VEGF-R, FGF-R, and PDGF-R growth factor receptors. These compds. were evaluated for their inhibitory properties toward VEGF-R2 (Flk-1/KDR), FGF-R1, PDGF-R.beta., p60c-Src, and EGF-R tyrosine kinases and their ability to inhibit growth factor-dependent cell proliferation. Structure-activity relationships of this new pharmacophore have been detd. at the level of kinase inhibition. Compds. contg. a propionic acid moiety at the C-3' position of the tetrahydroindole ring represented the most potent indolin-2-ones to inactivate the VEGF, FGF, and PDGF receptor kinases. The inhibitory activities of 3-[3-(2-carboxyethyl)-4,5,6,7-tetrahydro-1H-indol-2-ylmethylene]-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid against VEGF-R2 (Flk-1), 3-(2-[6-(2-methoxyphenyl)-2-oxo-1,2-dihydroindol-3-ylidenemethyl]-4,5,6,7-tetrahydro-1H-indol-3-yl)propionic acid against FGF-R1, and 3-[2-(5-bromo-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-4,5,6,7-tetrahydro-1H-indol-3-yl]propionic acid (I) against PDGF-R.beta. were 4, 80, and 4 nM, resp. However, all of these compds. were inactive when tested against the EGF-R tyrosine kinase. Compds. 3-[2-(2-oxo-1,2-dihydroindol-3-ylidenemethyl)-4,5,6,7-tetrahydro-1H-indol-3-yl]propionic acid (II) and I represented the most potent inhibitors of these classes to inhibit both biochem. kinase and growth factor-dependent cell proliferation for these three targets. In addn., compd. II was cocrystd. with the catalytic domain of FGF-R1 providing evidence to explain the structure-activity relation results. This study has provided evidence to support the potential of these new tyrosine kinase inhibitors for the treatment of angiogenesis and other growth factor-related diseases including human cancers.

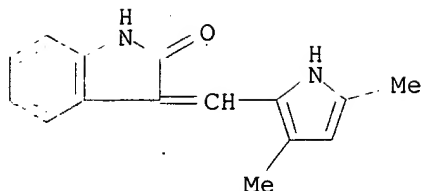
CC 1-3 (Pharmacology)

Section cross-reference(s): 2, 7, 27, 75

IT Enzyme functional sites
 (active; substituted [(tetrahydroindolyl)methylene]dihydroindolones as growth factor receptor inhibitors for **VEGF-R2 (Flk-1/KDR)** and **FGF-R1**, and **PDGF-R.beta.** tyrosine kinases and as inhibitors of growth factor-dependent cell proliferation)

IT **Vascular endothelial growth factor**
 receptors
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
 (gene KDR; substituted [(tetrahydroindolyl)methylene]dihydroindolones as growth factor receptor inhibitors for **VEGF-R2 (Flk-1/KDR)** and **FGF-R1**, and **PDGF-R.beta.** tyrosine kinases and as inhibitors of growth factor-dependent cell proliferation)

IT Structure-activity relationship



=> d .ca 113 1-7

L13 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:456819 HCAPLUS

DOCUMENT NUMBER: 133:84238

TITLE: 3-heteroarylidenyl-2-indolinone compounds for modulating protein kinase activity and for use in cancer chemotherapy

INVENTOR(S): Langecker, Peter J.; Shawver, Laura Kay; Tang, Peng Cho; Sun, Li

PATENT ASSIGNEE(S): Sugan, Inc., USA

SOURCE: PCT Int. Appl., 148 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2000038519 | A1 | 20000706 | WO 1999-US31232 | 19991230 |
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| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |

PRIORITY APPLN. INFO.: US 1998-114313 P 19981231

OTHER SOURCE(S): MARPAT 133:84238

AB 3-Heteroarylidenyl-2-indolinone compds. are provided that modulate the enzymic activity of protein kinases and therefore are expected to be useful in the prevention and treatment of protein kinase-related cellular disorders, e.g. cancer. Furthermore, these compds. are expected to enhance the efficacy of other chemotherapeutic agents, in particular, fluorinated pyrimidines, in the treatment of cancer.

IC ICM A01N043-38

ICS A61K031-40

CC 1-6 (Pharmacology)

Section cross-reference(s): 27, 63

IT Cell proliferation

Kidney, neoplasm

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|----------|-----------------|-------------|
| WO 9640116 | A1 | 19961219 | WO 1996-US8903 | 19960605 |
| W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IL, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, AM, AZ, BY | | | | |
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| US 5880141 | A | 19990309 | US 1995-485323 | 19950607 |
| CA 2192797 | AA | 19961219 | CA 1996-2192797 | 19960605 |
| AU 9660441 | A1 | 19961230 | AU 1996-60441 | 19960605 |
| AU 706597 | B2 | 19990617 | | |
| EP 769947 | A1 | 19970502 | EP 1996-918093 | 19960605 |
| EP 769947 | B1 | 20010502 | | |
| R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| BR 9606410 | A | 19971230 | BR 1996-6410 | 19960605 |
| JP 10504323 | T2 | 19980428 | JP 1996-501363 | 19960605 |
| EP 934931 | A2 | 19990811 | EP 1999-103667 | 19960605 |
| EP 934931 | A3 | 19991020 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI | | | | |
| JP 2000026412 | A2 | 20000125 | JP 1999-159567 | 19960605 |
| NO 9605377 | A | 19970212 | NO 1996-5377 | 19961213 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 1995-485323 | A 19950607 |
| | | | EP 1996-918093 | A3 19960605 |
| | | | JP 1997-501363 | A3 19960605 |
| | | | WO 1996-US8903 | W 19960605 |
| OTHER SOURCE(S): MARPAT 126:139901 | | | | |
| AB The present invention relates to org. mols. capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation. Representatives of the 5 different classes of compds. described are SU 4932 [3-(2-chloro-4-hydroxybenzylidenyl)-2-indolinone], SU 4312 [3-(4-dimethylaminobenzylidenyl)-2-indolinone], SU 5416 {3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone}, SU 5204 [3-(2-ethoxybenzylidenyl)-2-indolinone], and SU 4942 [3-(4-bromobenzylidenyl)-2-indolinone]. Diseases which these compds. and their pharmaceutically acceptable preps. may be effective against include arthritis, hepatic cirrhosis, diabetic nephropathy and psoriasis. | | | | |
| IC | ICM A61K031-40 | | | |
| | ICS C07C209-34 | | | |
| CC | 1-12 (Pharmacology) | | | |
| | Section cross-reference(s): 27, 63 | | | |
| IT | Epidermal growth factor receptors | | | |
| | Fibroblast growth factor receptors | | | |
| | Insulin receptors | | | |
| | Insulin-like growth factor I receptors | | | |
| | Platelet-derived growth factor receptors | | | |
| | RL: BSU (Biological study, unclassified); BIOL (Biological study) (prepn. of indolinones capable of modulating tyrosine kinase signal transduction) | | | |

L13 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:640690 HCAPLUS

DOCUMENT NUMBER: 127:314804

TITLE: Assays for KDR/FLK-1 receptor tyrosine kinase inhibitors, and use of the inhibitors for treatment of

vasculogenesis- and angiogenesis-related diseases
INVENTOR(S): Hirth, Klaus P.; McMahon, Gerald; Shawver, Laura K.

PATENT ASSIGNEE(S): Sugen, Inc., USA

SOURCE: PCT Int. Appl., 65 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 9734920 | A1 | 19970925 | WO 1997-US3378 | 19970304 |
| W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9720667 | A1 | 19971010 | AU 1997-20667 | 19970304 |
| PRIORITY APPLN. INFO.: | | | US 1996-621734 | 19960321 |
| | | | WO 1997-US3378 | 19970304 |

AB Processes are disclosed for the identification of compds. and pharmaceutical compns. capable of selectively and potentially inhibiting KDR/FLK-1 tyrosine kinase signal transduction in order to inhibit vasculogenesis and/or angiogenesis. The invention also relates to compds.

and compns. identified using the methods of the invention and the use thereof for the treatment of disease relating to inappropriate vasculogenesis and/or angiogenesis. The invention provides an assay cascade comprised of several "filter steps" of increasing selectivity which identify a limited subset of candidate compds. affecting the VEGF receptor on the mol. level.

IC ICM C07K002-00

ICS C07K014-705; C07K016-28; C12N005-06; C12N005-07; C12Q001-00; A16K031-00; A16K035-00; A16K039-395; G01N033-15; G01N033-48; G01N022-53

CC 1-1 (Pharmacology)

Section cross-reference(s): 63

IT Animal cell line

(EPH-4/VEGF; KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

IT Antibodies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (immobilized, to VEGF receptor; KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment

of vasculogenesis- and angiogenesis-related diseases)

IT Growth factor receptors

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(vascular endothelial growth factor, gene KDR; KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

IT Growth factor receptors
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(vascular endothelial growth factor, gene flt 1; KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

IT Receptors
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(vascular endothelial growth factor; KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

IT 127464-60-2, **Vascular endothelial growth factor**
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

IT 3359-49-7, SU 4928 5812-07-7, SU 4312 **62540-08-3**, SU 5208
91822-51-4, SU 4314 186611-03-0, SU 4932 186611-55-2, SU 4313
 197592-54-4, SU 0879 197592-55-5, SU 1076 197592-56-6, SU 1385
 197592-57-7, SU 1387 197592-58-8, SU 1393 197592-59-9, SU 1433
 197592-60-2, SU 1498 197592-61-3, SU 1835 197592-62-4, SU 4136
 197592-63-5, SU 4157 197592-64-6, SU 4161 197592-65-7, SU 4209
 197592-66-8, SU 4304 197592-67-9, SU 4328 197592-68-0, SU 4334
 197592-69-1, SU 4348 197592-70-4, SU 4929 197592-71-5, SU 4936
 197592-72-6, SU 4943 197592-73-7, SU 4945 197592-74-8, SU 5014
 197592-75-9, SU 5015 **204005-46-9**, SU 5416
 RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

IT 141350-03-0, Flt-1 **VEGF** receptor tyrosine kinase 150977-45-0,
 Flk-1/KDR **VEGF** receptor tyrosine kinase
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(KDR/FLK-1 receptor tyrosine kinase inhibitor identification assay, and use of compds. for treatment of vasculogenesis- and angiogenesis-related diseases)

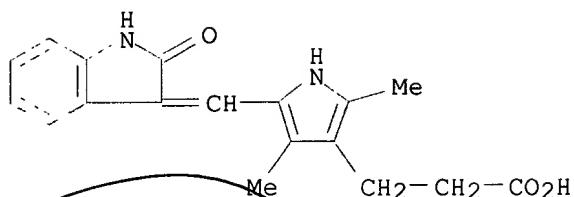
SOURCE: Congxin; Schlessinger, Joseph; Hubbard, Stevan R.;
 McMahon, Gerald; Tang, Peng C.
 PCT Int. Appl., 493 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 9807835 | A2 | 19980226 | WO 1997-US14885 | 19970821 |
| WO 9807835 | A3 | 19981001 | | |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 5942428 | A | 19990824 | US 1996-701191 | 19960821 |
| AU 9741603 | A1 | 19980306 | AU 1997-41603 | 19970821 |
| EP 931152 | A2 | 19990728 | EP 1997-939534 | 19970821 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| PRIORITY APPLN. INFO.: | | | US 1996-701191 | 19960821 |
| | | | US 1996-34168 | 19961219 |
| | | | WO 1997-US14885 | 19970821 |

OTHER SOURCE(S): MARPAT 128:164361
 AB The present invention relates to the 3-dimensional structures of a protein
 tyrosine kinase optionally complexed with one or more compds. Thus, a 310-amino acid fragment fibroblast growth factor receptor 1 (residues 456-765, FGFR1) was recombinantly prep'd. contg. the amino acid substitutions Cys488.fwdarw.Ala, Cys584.fwdarw.Ser, and Leu457.fwdarw.Val,
 and an addnl. 5 residues (Ser-Ala-Ala-Gly-Thr) at the N-terminus. X-ray crystallog. yielded the at. structural coordinates of cryst. FGFR1 and its
 complexes with adenylyl diphosphonate, 3-[(3-(2-carboxyethyl)-4-methylpyrrol-5-yl)methylene]-2-indolinone, or 3-[4-(4-formylpiperazine-1-yl)benzylidenyl]-2-indolinone. Two forms of cryst. FGFR1 were obtained: one form (designated C2-A form) with unit cell dimensions of a = 208.3, b = 57.2, c = 65.5.ANG. and .beta. = 107.2.degree., and another C2-B form with dimensions a = 211.6, b = 51.3, c = 66.1.ANG. and .beta. = 107.7.degree.. The overall structure of FGFR1 is bi-lobate. The N-terminal lobe of FGFR1 spans amino acid residues 456-567 and comprises
 a
 curled .beta.-sheet of five antiparallel strands and one .alpha.-helix. The C-terminal lobe spans amino acid residues 568-765 and comprises two .beta.-strands and seven .alpha.-helixes. The at. coordinates that
 define
 the structures of the protein tyrosine kinase and any of the compds.
 bound
 to it are pertinent to methods for detg. the 3-dimensional structures of protein tyrosine kinases with unknown structure and to methods that

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|---|----------|-----------------|------------|
| WO 9948868 | A2 | 19990930 | WO 1999-US6468 | 19990326 |
| WO 9948868 | A3 | 20000224 | | |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
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| AU 9933635 | A1 | 19991018 | AU 1999-33635 | 19990326 |
| EP 1066257 | A2 | 20010110 | EP 1999-915018 | 19990326 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| PRIORITY APPLN. INFO.: | | | US 1998-79713 | P 19980326 |
| | | | US 1998-80422 | P 19980402 |
| | | | US 1998-81792 | P 19980415 |
| | | | US 1998-82056 | P 19980416 |
| | | | US 1998-89397 | P 19980615 |
| | | | US 1998-89521 | P 19980616 |
| | | | US 1998-98783 | P 19980901 |
| | | | WO 1999-US6468 | W 19990326 |
| OTHER SOURCE(S): MARPAT 131:257441 | | | | |
| AB The invention relates to certain indolinone-based and pyrazolylamide-based compds., I and II, their method of synthesis, and combinatorial libraries consisting of the compds. [wherein AB = atoms to make up 1-2 fused and/or connected rings; R = arom. or heteroarom. ring which may form an addnl. ring by cyclization to the methylene group; R1, R2 = H, alkyl, (hetero)aryl or -aliph. ring, amino, NO2, halo, etc.; R3 = (un)substituted Ph; Z = (un)substituted (CH2)0-3; R4, R5 = H, alkyl, (hetero)aryl or -aliph., amine, ketone, etc.]. The invention also relates to methods of modulating the function of protein kinases using these compds., and methods of treating diseases by modulating the function of protein kinases and related signal transduction pathways. Data for prepn. and/or biol. activity are given, as well as the prepn. of various oxindole intermediates. For instance, the pyrazolecarboxamide deriv. III gave up to 70% inhibition of growth of Calu-6 human lung carcinoma cells as a xenograft in mice. As another example, the indolinone deriv. IV was prepd. by condensation of 6-(4-methoxyphenyl)-2-oxindole with 3,5-dimethyl-1H-pyrrole-2-carboxaldehyde in the presence of piperidine. Extensive tests of a few selected compds. against a variety of protein kinases are described. | | | | |
| IC | ICM C07D209-34 | | | |
| | ICS C07D403-06; C07D409-06; A61K031-40; A61K031-415 | | | |
| CC | 27-11 (Heterocyclic Compounds (One Hetero Atom)) | | | |
| | Section cross-reference(s): 1 | | | |
| IT | Blood vessel | | | |
| | (endothelium, inhibition of proliferation; prepn. of pyrazolecarboxylic acid amides and (arylmethylene)indolinones as | | | |



L11 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:147306 HCAPLUS

DOCUMENT NUMBER: 128:204803

TITLE: Indolinone combinatorial libraries and related products and methods for the treatment of disease

INVENTOR(S): Tang, Peng Cho; Sun, Li; McMahon, Gerald; Hirth, Klaus

PATENT ASSIGNEE(S): Peter; Shawver, Laura Kay; et al.
Sugen, Inc., USA; Tang, Peng Cho; Sun, Li; McMahon, Gerald

SOURCE: PCT Int. Appl., 293 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

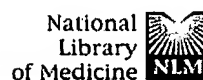
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 9807695 | A1 | 19980226 | WO 1997-US14736 | 19970820 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| CN 1155838 | A | 19970730 | CN 1996-190616 | 19960605 |
| EP 929520 | A1 | 19990721 | EP 1997-939480 | 19970820 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| US 6147106 | A | 20001114 | US 1997-915366 | 19970820 |
| JP 2001503736 | T2 | 20010321 | JP 1998-510973 | 19970820 |
| AU 9741556 | A1 | 19980306 | AU 1997-41556 | 19970821 |
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| US 1997-45566 P 19970505 | | | | |
| US 1997-45714 P 19970505 | | | | |
| US 1997-45715 P 19970505 | | | | |

09, 333, 703



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Chin Med J (Engl). 1998 May;111(5):398-403.
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PMID: 10373307 [PubMed - indexed for MEDLINE]

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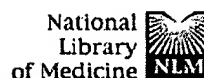
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PMID: 10371763 [PubMed - indexed for MEDLINE]

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Loop III region of platelet-derived growth factor (PDGF) B-chain mediates binding to PDGF receptors and heparin.

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